ART 34 AMDT

CLAIMS

1. Recombinant proteins comprising two superdomains, separated by a spacer sequence (linker), obtained combining the HL and K1-K4 domains of HGF and/or MSP α chains, according to general formula (I):

[A] - B - [C] - (D)y (I)

in which

[A] corresponds to the sequence $(LS)_m$-HL-K1-$(K2)_n$-$(K3)_o$-$(K4)_p$

wherein (the numbering of the following amino acids refers to the HGF and MSP sequences as reported in Fig. 1 and 2, respectively):

LS is an amino acid sequence corresponding to residues 1-31 of HGF or 1-18 of MSP;

HL is an amino acid sequence starting between residues 32-70 of HGF α chain and ending between residues 96-127 of the identical chain; or it is an amino acid sequence starting between residues 19-56 of MSP α chain and ending between residues 78-109 of the identical chain;

K1 is an amino acid sequence starting between residues 97-128 of HGF α chain and ending between residues 201-205 of the identical chain; or it is an amino acid sequence starting between residues 79-110 of MSP α chain and ending between residues 186-190 of the identical chain;

K2 is an amino acid sequence starting between residues 202-206 of HGF α chain and ending between residues 283-299 of the identical chain; or it is an amino acid sequence starting between residues 187-191 of MSP α chain and ending between residues 268-282 of the identical chain;

K3 is an amino acid sequence starting between residues 284-300 of HGF α chain and ending between residues 378-385 of the identical chain; or it is

an amino acid sequence starting between residues 269-283 of MSP α chain and ending between residues 361-369 of the identical chain;

K4 is an amino acid sequence starting between residues 379-386 of HGF α chain and ending between residues 464-487 of the identical chain; or it is an amino acid sequence starting between residues 362-370 of MSP α chain and ending between residues 448-481 of the identical chain;

m, n, o, p are 0 or 1;

the sum n + o + p is an integer from 1 to 3 or 0, with the proviso that n ≥ o ≥ p;

B is the sequence $[(X)_q Y]_r$, wherein X = Gly and Y = Ser, or Cys, or Met, or Ala;

q is an integer from 2 to 8;

r is an integer from 1 to 9;

[C] corresponds to the sequence HL-K1-$(K2)_s$-$(K3)_t$-$(K4)_u$

wherein HL, K1-K4 are as defined above,

s, t, u are 0 or 1; the sum s + t + u is an integer from 1 to 3 or 0, with the proviso that s ≥ t ≥ u;

D is the sequence W-Z, wherein W is a conventional proteolytic site, Z is any tag sequence useful for the purification and detection of the protein; y is 0 or 1.

2. Recombinant proteins according to ~~claims 1-2,~~ claim 1 in which the HL domain is a sequence of HGF α chain ranging from amino acids 32 to 127, or a sequence of MPS α chain ranging from amino acids 19 to 98; the K1 domain is a sequence of HGF α chain ranging from amino acids 128 to 203, or a sequence of MPS α chain ranging from amino acids 99 to 188; the K2 domain is a sequence of HGF α chain ranging from amino acids 204 to 294,

or a sequence of MPS α chain ranging from amino acids 189 to 274; the K3 domain is a sequence of HGF α chain ranging from amino acids 286 to 383, or a sequence of MPS α chain ranging from amino acids 275 to 367; the K4 domain is a sequence of HGF α chain ranging from amino acids 384 to 487, or a sequence of MPS α chain ranging from amino acids 368 to 477.

3. Recombinant proteins according to ~~claims 1-2~~ claim 1 or 2 of formula (II):

LS_{MSP}-HL_{MSP}-$K1_{MSP}$-$K2_{MSP}$-L-HL_{HGF}-$K1_{HGF}$-$K2_{HGF}$-D (II)

in which LS_{MSP} is the sequence 1-18 of MSP, HL_{MSP} is the sequence 19-56 of MSP, $K1_{MSP}$ is the sequence 99-188 of MSP, $K2_{MSP}$ is the sequence 189-274 of MSP, HL_{HGF} is the sequence 32-127 of HGF, $K1_{HGF}$ is the sequence 128-203 of HGF, $K2_{HGF}$ is the sequence 204-294 of HGF, L is the sequence $(Gly_4Ser)_3$, D is the sequence Asp_4-Lys-His_6.

4. Recombinant proteins according to ~~claims 1-2~~ claim 1 or 2 of formula (III):

LS_{HGF}-HL_{HGF}-$K1_{HGF}$-$K2_{HGF}$-L-HL_{HGF}-$K1_{HGF}$-$K2_{HGF}$-D (III)

in which HL_{HGF}, $K1_{HGF}$, $K2_{HGF}$, L and D are as defined in claim 4, LS_{HGF} is the sequence 1-31 of HGF.

5. Nucleotide sequences encoding for the recombinant proteins of ~~claims~~ claims 1-2 ~~1-5~~.

6. Expression vectors comprising the nucleotide sequences of claim 5.

7. Prokaryotic or eukaryotic host cell transformed with the expression vector of claim 6.

8. Process for preparing the recombinant proteins of ~~claims 1-4~~ claim 1, which comprises the following steps:

a) construction of DNA encoding the desired protein;

b) insertion of DNA in an expression vector;

c) transformation of a host cell with recombinant DNA (rDNA);

d) culture of the transformed host cell so as to express the recombinant protein;

e) extraction and purification of the produced recombinant protein.

9. Process according to claim 8, wherein the host cell is kidney epithelial BOSC cell or SF9 insect cell.

10. Recombinant proteins of ~~claims 1-4~~ Claim 1 for use as therapeutic agents.

11. Use of recombinant proteins of ~~claims 1-4~~ Claim 1 in the manufacture of a medicament for the prevention or treatment of chemotherapeutic-induced toxicity.

12. Use according to claim 9, wherein the chemotherapeutic-induced toxicity is myelotoxicity, kidney toxicity, neurotoxicity, mucotoxicity and hepatotoxicity.

13. Pharmaceutical compositions containing an effective amount of the recombinant proteins of ~~claims 1-4~~ Claim 1, in combination with pharmacologically acceptable excipients.